Adverse events and residual lesion rate after cold endoscopic mucosal resection of serrated lesions ≥10 mm

Connor D. McWhinney, BS

Krishna C. Vemulapalli, MBBS, MPH

Ahmed El-Rahyel, MD

Noor Abdullah

Douglas K. Rex, MD

Division of Gastroenterology/Hepatology, Indiana University School of Medicine

Indianapolis, Indiana

Correspondence:

Douglas K. Rex

550 N. University Blvd.

Suite 4100

Indianapolis, IN 46202

drex@iu.edu

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Abstract

Background and Aims: Cold endoscopic mucosal resection (EMR) is being increasingly used for large serrated lesions. We sought to measure residual lesion rates and adverse events after cold EMR of large serrated lesions.

Methods:

In a single academic center, we retrospectively examined a database of serrated class lesions ≥ 10 mm removed with cold EMR for safety and efficacy.

Results:

Five hundred and sixty-six serrated lesions ≥10 mm in size were removed from 312 patients. We successfully contacted 223 patients (71.5%) with no reported serious adverse events that required hospitalization, repeat endoscopy, or transfusion. The residual lesion rate per lesion at first follow-up colonoscopy was 18 out of 225 (8%; 95% CI, 5-12.1). Lesions with residual were larger at polypectomy compared with lesions without recurrence (median, 23 mm vs 16 mm, p=0.017).

Conclusion:

Cold EMR appears to be safe and effective for the removal of large serrated lesions.

Introduction

Sessile serrated lesions (SSLs) ≥10 mm in size appear ideal for endoscopic mucosal resection (EMR), and resection without electrocautery (cold resection). In a study using standard endoscopic resection techniques, serrated class lesions 10 to 20 mm in size were ineffectively

resected in almost 50% of cases and were 4 times more likely to be incompletely resected compared with adenomas[1]. However, in 3 studies using EMR with electrocautery for large serrated lesions, numerical rates of complete resection at follow-up were better for serrated class lesions than conventional adenomas of similar size[2-4]. Presumably, the use of EMR with a submucosal contrast agent, in combination with a high-definition colonoscope, effectively allowed endoscopists using EMR to identify all serrated glands and remove them.

An initial study by Tutticci and Hewett[5] found that the removal of serrated class lesions could be effectively performed using cold EMR techniques, with a residual lesion rate <1%. In cold EMR, the lesion is injected submucosally with fluid containing a contrast agent and then removed using a diminutive snare, typically using piecemeal technique and without electrocautery. Cold techniques without submucosal injection have also been applied to large serrated lesions, with a low recurrence rate[6]. However, the number of patients reported with cold piecemeal resection of large serrated lesions without submucosal injection is smaller. In general, cold resection techniques appear safer than resection techniques using electrocautery[5-12], with a much reduced or negligible risk of delayed postpolypectomy hemorrhage, and negligible risk of postpolypectomy syndrome and perforation.

In this report, we describe the adverse event rate in patients undergoing cold EMR and having at least a 30-day follow-up, and the rate of residual polyp in patients undergoing follow-up at our center.

Methods:

Given the initial reports of cold EMR, we converted most serrated lesion resections to cold methods in February 2016. We did not use cold EMR for all serrated class lesions ≥10 mm after this date (some were removed by cold piecemeal resection without injection, and some serrated class lesions ≥20 mm were removed using hot EMR), but most serrated resections ≥10 mm were removed by cold EMR. We performed a retrospective review of a prospectively maintained database of lesions ≥10 mm resected by the senior author (D.K.R) between February 2016 and December 2019 using cold EMR at an academic university hospital outpatient endoscopy unit. The Institutional Review Board at Indiana University granted permission to review the database for the study.

We included serrated class lesions ≥10 mm and excluded conventional adenomas. Patients were included irrespective of their anticoagulation status. Some patients had other lesions that were removed using electrocautery during the same procedure as the cold EMR and we report the adverse events rates separately for this group. We attempted telephone contact to all patients at least 30 days after the procedure to ascertain adverse events. In addition, all patients undergoing a follow-up examination at our center were queried for adverse events after the EMR.

Colonoscopic procedures

All procedures were performed using high definition Olympus 190 series (Olympus Corp, Central Valley, Pa, USA) colonoscopes, and a few cases with 180 series instruments. Cold EMR was performed by injecting either hydroxyethyl starch mixed with a contrast agent (indigo

carmine or methylene blue) or Eleview (Aries Pharmaceutical, San Diego, Calif, USA). Epinephrine was not added to the injectate. The snares used were primarily Exacto (U.S. Endoscopy, Mentor, Ohio, USA) and the Captivator Cold (Boston Scientific, Marlborough, Mass, USA). The general strategy was to resect piecemeal and include a wide margin (up to ≥10 mm) of normal tissue around the lesion edge. Lesions were nearly all removed piecemeal. If the snare became stuck on submucosal tissue, mechanical traction was used to pull the snare through. If intraprocedural arterial bleeding or rapid venous bleeding occurred and persisted, one or more clips were placed on the site of active bleeding. Lesions that were referred were often tattooed. We typically did not tattoo lesions, particularly in SPS patients with multiple lesions. We did record size and location of all lesions. Patients were asked to follow up for surveillance after 6 months to 3 years, depending on the size, number, and pathology of the lesions. We located scars by inspection in white light with full colonic distension. Endocuff Vision (Olympus Corp, Center Valley, Pa, USA) was used routinely in follow-up examinations). Retroflexion was used in the right and transverse colons as needed to facilitate scar identification. Resection sites were inspected with high-definition colonoscopes and near focus when available and with both white light and narrow band imaging (NBI). Residual serrated lesion was identified by the surface texture and pit differences compared with normal and scar tissue and recognized as residual serrated lesion by features consistent with Type 1 lesions of the NICE (NBI International Colorectal Endoscopic classification) [13]. Biopsy specimens were taken from sites inconsistently and primarily from referred patients traveling significant distances, for whom follow-up at our center was less likely. Biopsies were considered impractical in SPS patients with several or more resections, based on the perceived time and cost of biopsy of

several or numerous sites. If no scar could be identified at follow-up, we excluded the lesion from calculation of the recurrence rate.

The primary outcomes were the number of patients who reported experiencing adverse events within 30 days of the index procedure, and residual lesion rate per polyp at first follow-up colonoscopy. Adverse events were defined as bleeding, cramping, emergency department visit/hospital visits, or any abdominal pain. We defined residual lesion as either visual confirmation of polyp tissue or histological biopsy of the polypectomy scar site indicating serrated histology.

Statistical analysis

We report descriptive characteristics for patients and polyps. For the primary outcomes of adverse events and residual lesion at first follow-up, we report 95% confidence intervals. We used Mann-Whitney U test to compare index polyp size between recurrent and nonrecurrent lesions (level of significance, 5%). All analyses were performed using SPSS, Version 26 (IBM, Armonk, NY, USA).

Results:

During the study interval, 566 eligible lesions were removed from 312 patients by cold EMR at 351 examinations. The mean age of the cohort was 62.5 (±10.5) years, and 69.9% were women (Table 1). The mean lesion size was 17.2 mm (±6.5), and 88.3% were located proximal to

splenic flexure. Five hundred twenty-two were histologically sessile serrated lesions (SSL), 36 were hyperplastic polyps (HP) and 8 were traditional serrated adenomas (TSA).

Two hundred twenty-three patients (71.5%) of the 312 who underwent cold EMR were contacted to ascertain adverse events. Of these, 205 had no other colorectal lesion removed using electrocautery at the index procedure. The adverse event rate in this group was 3.9% (95% CI, 1.9%-7.2%), but none of the events were serious (bleeding which stopped without any intervention, n=4; persistent pain relieved without intervention, n=1; felt foggy after procedure, n=1; visited emergency department for arrhythmia after the procedure with no intervention needed, n=1; minor aspiration during procedure without any intervention, n=1).

Of the 18 patients who had cold EMR of a serrated lesion ≥10 mm and also had another lesion in the colon removed using electrocautery, there were two adverse events (11.1%) (95% CI, 2.4%-31.1%) (postprocedure chills, n=1; bleeding that stopped without any intervention, n=1). To our knowledge, no patient undergoing cold EMR required hospitalization, transfusion, antibiotic treatment or repeat colonoscopy to treat bleeding.

Among the 312 study patients, 110 have thus far undergone follow-up colonoscopy at our center (median follow-up time, 12.4 months) and were included in the calculation of recurrence. Five additional patients underwent surveillance but were not included in the calculation of residual lesion. Four of these had single lesions resected and no scar or residual lesion was found at surveillance. The fifth excluded patient had 64 lesions resected, and it was not feasible to match the resected lesions with the scars. Of the 225 index lesions removed from these 110 patients,

the residual lesion rate at first follow-up was 8% (18/225; 95% CI, 5-12.1). This included a visible residual lesion in 13, and 5 lesions with no visible residual lesion but a positive scar biopsy. The median size of index lesions with residual lesion was 23 mm compared with 16 mm in index lesions without residual (p=0.017).

Seventy-six subjects were diagnosed with serrated polyposis syndrome (SPS) in this cohort. These 76 patients had between 1 and 9 EMRs, except one who had 64 EMRs. The mean size of the lesions in patients with SPS was 18.5 mm compared with 16.4 mm in patients without SPS (p=0.09). The mean number of study lesions from SPS patients was 3.5 and 1.3 in patients without SPS (P=0.012). In total, 263 of the 566 study lesions were removed from SPS patients (46.5%).

Discussion

In this report, we describe our initial experience with adverse events and residual lesion after cold EMR of serrated class lesions ≥10 mm in size. More than 90% of the lesions were called SSLs by our pathologists, with much smaller numbers of HPs and TSAs. There is significant interobserver variation between pathologists in the differentiation of SSLs from hyperplastic polyps (HPs), and postpolypectomy surveillance guidelines recommend that HPs ≥10 mm can be treated as SSLs[14], and warrant closer follow-up than HPs <10 mm in size[14]. Thus, lesions ≥10 mm and interpreted pathologically as hyperplastic may have clinical significance.

Our experience confirms that the rate of adverse events after cold EMR of SSLs is minimal and appears clinically insignificant compared with historical reports of hot EMR of lesions ≥10

mm[15], and particularly those ≥20 mm[16-19]. Arguably, there were no clinically significant adverse events from cold EMR in our study. Thus, we can confirm that cold EMR is a safe technique.

From an endoscopic perspective, SSLs appear to be ideal candidates for cold EMR compared with conventional adenomas. SSLs, if not subjected to biopsy or partial resection, are nearly always devoid of submucosal fibrosis (Figure 1). Anecdotally, they lift extremely well as a class of lesions compared with conventional adenomas, when submucosal injection is performed, almost regardless of what injection fluid is used. During cold EMR, they separate easily from the submucosal tissue, and essentially never have either the bulk nor the fibrosis seen in many conventional adenomas that may require electrocautery for successful submucosal snare transection.

The rate of residual lesion that we identified in this study is higher than some recent reports[5, 6, 20], and comparable to the rates of residual lesion we have described for serrated lesions removed by hot EMR at our own center[2]. The reasons for the higher residual lesion rate of SSLs in this study are uncertain and are potentially technical in nature. For example, we did not include epinephrine in the injection fluid. Recent studies have shown that intraprocedural hemorrhage is associated with an increased risk of residual lesion[12], and anecdotally cold resection without epinephrine is clearly associated with a bloodier intraprocedural endoscopic field than when epinephrine is included in the injectate. Further, we did encounter some cases of persistent bleeding that was more than generalized oozing and included visible arterial hemorrhage, which we treated in some cases by clip application (Table 1). Thus, although no randomized controlled trial has demonstrated that inclusion of epinephrine in the injectate is associated with a lower risk of residual polyp, such a trial may be warranted, and there is at least some evidence suggesting

that inclusion of epinephrine is associated with a lower residual lesion rate[21]. Despite these comments about the potential benefits of including epinephrine in the submucosal injection fluid, our anecdotal experience is that the venous oozing that occurs during cold EMR without epinephrine, although clearly increased compared with cold EMR with epinephrine, is typically self-limited and does not interfere significantly with visibility during resection. Second, although we used diminutive snares throughout the study period, we did allow mechanical transection of the tissue by pulling it against the colonoscope when the snare became stuck on the submucosa. This practice generally leads to the production of "submucosal cords." Submucosal cords in the cold snaring of diminutive polyps have not been associated with any significant occurrence of residual polyp tissue on the tip of the cord [22]. However, some expert investigators and proponents of cold EMR anecdotally try to avoid cord creation during cold EMR[23]. A prospective study examining whether such cords created during cold EMR harbor residual polyp tissue may be warranted. We tried to resect the lesions with a substantial margin of normal tissue and inspected the lesion margins carefully for residual serrated glands, which seem to be readily apparent after contrast injection and inspection using a high definition colonoscope. It is conceivable that other technical considerations such as aggressive endoscopic washing of the defect during the procedure might lower the residual lesion rate, but this remains uncertain. Another factor that could affect the residual lesion rate in our study is that a substantial percentage of the patients were referred for resection, and almost all of these patients had the lesion previously biopsied. Biopsy of SSLs, particularly when flat, often results in obvious tacking of the lesion to the submucosa at the site of the biopsy, which might interfere with the completeness of resection using either hot or cold EMR methods. Another potential contributor to the higher rate of residual polyp is that the median follow-up in this study was 12.4 months, which is longer than

the 6 months in some other studies. This longer interval might allow more time for a visible residual lesion to develop. Finally, the higher residual rates could reflect differences in inspection methods of the polypectomy scar at follow-up. Currently, all these explanations are speculative. Overall, given the residual lesion rates previously reported for serrated class lesions 10 to 20 mm using standard polypectomy methods[1], and the residual lesion rates for serrated class lesions associated with hot EMR[2-4], the residual lesion rate reported here, though numerically higher than some other recent studies of cold EMR, appears acceptable. However, controlled trials comparing hot and cold EMR of both serrated class lesions and conventional adenomas seem warranted.

Limitations of this study include that we did not biopsy all of the EMR scars at follow-up, so that the reported rate of residual lesion of 8% likely modestly understates the true rate of residual polyp. Further, many patients in the study have not undergone follow-up yet, or have had follow-up at another center. We did not ask routinely ask patients to return at 6 months for follow-up after piecemeal EMR, particularly for lesions <20 mm in size[24], and many were asked to return in 3 years despite piecemeal resection. Some lesions in the 20 to 30 size range were asked to return in 1 year rather than 6 months[25]. Patients with SPS might be followed at intervals of 3 months to 2 years[26], depending on the progress in reducing of polyp burden. For these reasons, many patients in the series have not had follow-up at our center at this writing. Further, early in the series we did not remove all lesions by cold EMR, with some tendency to use hot EMR in very large and referred lesions, so that early on there was some selection bias in which lesions were treated by EMR. Later we moved to cold EMR for the entire set of sessile serrated lesions. With regard to adverse events, the study is limited in that about one-third of patients were not successfully contacted. Another limitation is that we did not record which cold snare

was used in the resections, so no data comparing the performance of different cold snares are available. Finally, the study is from a single center and single endoscopist, and therefore the results may not be generalizable.

In conclusion, in a largeseries of cold EMR of serrated lesions ≥10 mm in size, we found no significant adverse events, a negligible rate of adverse events and an acceptably low rate of residual polyp at first follow-up. Although randomized controlled trials using an endpoint of residual lesion at follow-up still seem warranted, our results support the continued expansion of cold EMR in the treatment of sessile serrated lesions.

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Figure legend

Figure 1 Cold endoscopic mucosal resection of a sessile serrated lesion. A, 17-mm flat sessile serrated lesion when first visualized, with mucus cap. B, Same lesion after subucosal injection including indigo carmine as contrast agent. *Arrows* point to the lesion margin. C, Cap cold snare (Boston Scientific, Marlborough, Mass, USA) positioned to take first piece of lesion. *Arrow*

points to margin of lesion. Note several mm margin of normal tissue in snare. D, First piece of lesion has been removed. Snare positioned to take second piece of tissue. *Arrow* is on lesion margin. Note margin of normal tissue in snare. E, Residual serrated glands on the margin *(arrows)*. Note margin of normal tissue in the resection. F, The defect after resection. *Arrows* point to submucosal cords that developed during resection.

Table 1. Patient and polyp characteristics at index procedure and outcomes

Male gender, n (%)	94 (30.1%)
Average age, years ± SD	62.5 ± 10.5
Average polyp size, mm (SD)	17.2 (6.5)
No. of polyps clipped, n (%)	18 (3.2)
Polyp pathology SSP HP TSA	 522 (92.2) 36 (6.4) 8 (1.4)
Polyp location, n (%) Right colon (cecum, ICV, Ascending) Transverse (hepatic flexure, transverse, splenic flexure Left colon (descending, sigmoid, rectum)	 296 (52.3) 204 (36.0) 66 (11.7)
Cytological dysplasia, n (%)	17 (3)
Number of patients contacted for follow-up regarding adverse events, n (%) Average time between procedure and time of contact, months (min-max) Adverse events w/o electrocautery, n/N (%) Adverse events w/electrocautery, n/N (%)	223 (71.5) 13.4 (1.1-43.9) 8/205 (3.9) 2/18 (11.1)
Residual lesion rate per polyp, n/N (%)	18/225 (8.0)

HP, Hyperplastic polyp; ICV, Ileocecal valve, SSP, Sessile serrated polyp; TSA, Traditional serrated adenoma